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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/464,795	ZHANG ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,40,41,45,46,49 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,40,41,45,46,49 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed November 18, 2005 (hereinafter referred to as "the response") has been entered. Claims 38, 40, 45, and 65-68 have been amended. Claims 43 and 80 have been cancelled.

Accordingly, Claims 38, 40, 41, 45, 46, 49, and 65-68 remain pending in the instant application.

The rejection of Claim 80 under 35 U.S.C. 101 is withdrawn in view of the cancellation of this claim.

The rejection of Claim 80 under 35 U.S.C. 102(b) is withdrawn in view of the cancellation of this claim.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 18, 2005 has been entered.

Utility

Claims 38, 40, 41, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

Applicants' arguments have been fully considered, but do not overcome the standing grounds of rejection.

At page 6 of the response, although the claims have now been amended to recite "a promoter" derived from a stress-inducible gene, Applicants continue to argue the prior claim language of "control

element." Therefore, to clarify the rejection of record, the arguments are first addressed in view of the prior claim language directed to "control elements."

At page 6 of the response, Applicants assert that the amendment to recite the term "promoter" instead of "control element" fully addresses the utility rejection because "[i]t is abundantly plain to the skilled artisan that a promoter represents native gene expression. No support is offered for this assertion. The term "promoter" covers minimal promoters, truncated promoters, and promoters lacking their endogenous inducible elements. Thus, the presence of a "promoter" as broadly defined, would not represent native gene expression.

At page 6 of the response, Applicants assert that the Office has improperly construed the claims because "[t]he specification clearly and unambiguously defines the term 'control elements derived from a stress-inducible gene' to encompass only control elements that regulate transcription of at least one stress-inducible gene(s)." Not true. The express teachings with regard to the term "control elements" were acknowledged at pages 3-4 of the prior Office Action (final rejection, mailed 5/17/05) and are reiterated hereinbelow, and the term simply does not "encompass only control elements that **regulate transcription**" (emphasis added) as Applicants now assert.

With regard to the control element recited in the claims, the specification discloses the following at page 33:

> "The control element (e.g., a promoter) may be from the same species as the transgenic animal (e.g., mouse promoter used in construct to make transgenic mouse), from a different species (e.g., human promoter used in construct to make transgenic mouse), or a mixed control element (e.g., some control elements from a mouse promoter combined with some control elements of a human promoter)." Specification at page 33, lines 26-30.

The specification further discloses, at pages 11-12, that the "control element derived from a ... stress-inducible gene" may be as follows:

> "Typical control elements or expression control elements or regulatory sequences, include, but are not limited to transcription promoters, transcription enhancer elements, transcription termination signals, polyadenylation sequences (located 3' to the

> translation stop codon), sequences for optimization of initiation of translation (located 5' to the coding sequence), translation enhancing sequences, and translation termination sequences. Transcription promoters can include inducible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), repressible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), and constitutive promoters.
>
> Expression enhancing sequences typically refer to control elements that improve transcription or translation of a polynucleotide relative to the expression level in the absence of such control elements (for example, promoters, promoter enhancers, enhancer elements, and translational enhancers (e.g., Shine and Delagarno [sic] sequences))." Specification at pages 11-12.

Thus, in view of the specification's own definition the term "control element" does **not** "encompass only control elements that **regulate transcription**" (emphasis added) as Applicants now assert. As a first example, "sequences for optimization of initiation of translation" **do not regulate transcription.** As a second example, "translation enhancing sequences" **do not regulate transcription.** As a third example, "translation termination sequences" **do not regulate transcription.** Thus, Applicants' arguments are quite contrary to the teachings of the specification.

At page 6 of the response, Applicants state that "[i]nterestingly, the Examiner acknowledges later in the Office Action that the claims are not so broad as to cover control elements unrelated to stress-related genes." This appears to imply that the Examiner suggested the contrary position elsewhere in the Office Action. Such is not the case. Applicants appear to be confusing promoters with control elements. They are not equivalent. As stated in the prior Office Action, the claims cover the use of expression cassettes **having any promoter at all.** The claims do not recite promoters, only control elements. The mere presence of a polyadenylation signal "derived from a first stress-inducible gene" and another identical polyadenylation signal "derived from a second stress-inducible gene" would be sufficient to meet the claim limitations (Claim 38) and would be induced by **nothing**. See the specification at page 11, lines 24-26 which states that "[t]ypical control elements ... include ... polyadenylation sequences." The promoter can be any promoter at all. **There is nothing in the claim that limits the promoter (or even**

requires a promoter). The promoter, if one is even present, is not required to be derived from a stress-inducible gene. Applicants arguments are far afield from that which is claimed.

From this point forward, the response will be addressed only as it applies to the present claim language, directed to "promoters."

At page 7 of the response, Applicants assert that when the claims are properly construed, it is clear that what is meant by a promoter derived from a stress-inducible gene is a promoter that regulates transcription of a native stess-inducible gene. Regardless, the issue is not whether the stress-inducible gene is a native gene or not (it is clear that it is), but whether the promoter is present in its **native context.** The promoter must necessarily be **truncated** to insert it into the expression vector. As such, depending on where the truncation is made, variable portions of important regulatory elements may either be included or excluded from the construct. There is nothing in the claims that requires the inclusion of any particular regulatory elements beyond a basal or minimal promoter structure. Furthermore, there is no specific guidance on which portions should be included or which portions can be excluded (and still have a relevant experimental system). Thus, the relevance of the experimental system is highly dependent on the retention of all the relevant **native** regulatory regions that modulate promoter function.

At page 7 of the response, Applicants continue to argue that *in vivo* imaging provides an extremely powerful tool for studying gene expression. Be that as it may, the specification is clear that the intention is to create a construct and experimental system that recapitulates **native gene expression,** not gene expression in an artificial context. The specification does not provide specific guidance for creating constructs, within the scope of the claims, that have this utility.

At page 8 of the response, Applicants continue to assert that when the claims are properly construed, they do not include any species that lack utility. This issue has already been addressed at length.

At page 8 of the response, Applicants assert that there is a well established utility for using the claimed subject matter to study gene expression by *in vivo* imaging. Applicants are reminded that they need not rely upon a "well established" utility for studying gene expression, because the specification **asserts** this utility and this has already been acknowledged in the prior Office Actions. The problem is that the asserted utility of using the mouse or method to study gene expression applies only to those experimental systems that recapitulate **native** gene expression, and the claims are not directed to/limited to such constructs/experimental systems.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 38, 40, 41, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advance in the prior Office Actions of 2/1/01, 9/13/01, 8/27/02, 5/21/03, 10/5/04, 5/17/05, 10/31/05, and as further discussed herein, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At page 9 of the response, Applicants assert that all that is required is that the specification reasonably convey possession of the invention. Applicants further assert that the specification need not describe nucleotide sequences. The rejection of record does not pertain to nucleotide sequences. However, the specification makes it clear that the desired goal of the invention is to prepare contructs relevant to native gene expression in an *in vivo* context and then to use those constructs to observe the

effects of various treatments or agents on the promoter activity, but the specification has not described those constructs that will provide for native gene expression. The claims encompass mice comprising transgene constructs that comprise a wide variety of regulatory elements from stress-inducible genes, as discussed above (ranging from a minimal promoter to a 10Kb upstream region or larger, as suitable to the expression vector), but there is insufficient description of constructs that provide for native gene expression.

At page 10 of the response, Applicants assert that the claimed transgenic animals must be obtained using the particularly specified method. Applicants further argue that product-by-process claims are subject to a written description test much different from other product claims. Applicants refer to MPEP 2163 for stating that "...where the process has actually been used to produce the product, the written description requirement for a product-by-process claim is clearly satisfied." This quote does not pertain to the instant disclosure because the instant disclosure does not describe a process that "has actually been used to produce the product." No working examples are present in the specification, so it cannot be said that "the process has **actually** been used to produce the product" (emphasis added).

Enablement

Claims 38, 40, 41, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advance in the prior Office Actions of 2/1/01, 9/13/01, 8/27/02, 5/21/03, 10/5/04, 5/17/05, 10/31/05, and as further discussed herein, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' arguments with regard to enablement, at pages 11-12 of the response, are identical to those presented at pages 7-9 of the reponse filed 2/18/05. These arguments have already been considered

and addressed and are not found persuasive for the reasons set forth at pages 7-10 of the Office Action mailed 5/17/05.

Thus, the rejections are maintained, for reasons of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38, 40, 41, 45, 46, 49, and 65-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38, 40, 41, 45, 46, 49, and 65-68 are indefinite in their recitation of "said second control element" (in Claim 38) because the term lacks antecedent basis.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER